# Polymorphisms of the DNA Repair Gene *XRCC1* and Lung Cancer Risk

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## Abstract

**We explored the association between polymorphisms of the DNA repair gene *XRCC1* (codons 194, 280, and 399) and lung cancer risk in a case-control study nested within a cohort of tin miners. Cases were those diagnosed with lung cancer over 6 years of follow-up ($n = 108$). Two controls, matched on age and sex, were selected for each case by incidence density sampling. Of the three polymorphisms, only the *XRCC1* Arg280His allele was associated with increased lung cancer risk (odds ratio, 1.8; 95% confidence interval, 1.0–3.4) after adjustment for radon and tobacco exposure. In addition, individuals with the variant Arg280His allele who were alcohol drinkers seemed to be at higher risk for lung cancer compared with those with the homozygous wild-type genotype. Conversely, individuals with the variant Arg194Trp allele who were alcohol drinkers seemed to be at lower risk for lung cancer compared with those with the homozygous wild-type genotype. Polymorphisms of *XRCC1* appear to influence risk of lung cancer and may modify risk attributable to environmental exposures.**

## Introduction

There is considerable evidence that DNA repair capacity is genetically determined. Consequently, DNA repair enzyme gene polymorphisms, which may alter the function or efficiency of DNA repair, may contribute to cancer susceptibility (1–7). *XRCC1*[2] was originally discovered in radiation-sensitive mutants and assigned to the double-strand break/recombination pathway of DNA repair (8). Genetic polymorphisms of the DNA repair gene *XRCC1* have been identified at codons 194, 280, and 399 (9). These polymorphisms occur at residues that are identical in human, hamster, and mouse, suggesting that these amino acids are evolutionarily conserved (9, 10). A BCRT domain found in many proteins responsive to DNA damage with cell cycle checkpoint functions has also been identified in XRCC1 (11). XRCC1 is thought to form protein complexes with DNA ligase III via the BCRT domain in its COOH terminus and with DNA polymerase $\beta$ via its $NH_2$-terminal domain to repair gaps left during base excision repair (12). Because amino acid residues at the protein-protein interfaces of multiprotein complexes and residues involved in the active sites play a role in enzyme function, it is possible that the *XRCC1* polymorphisms may result in altered efficiency of the protein. A recent report by Lunn *et al.* (13) measuring the prevalence of aflatoxin B1 adducts in placental DNA from 120 Taiwanese women suggested that the *XRCC1* codon 399 polymorphism may result in deficient DNA repair.

The subjects in this study are miners for the YTC in China. The incidence rates of lung cancer are extraordinarily high in this population. Males >40 years of age with underground mining experience have a crude annual incidence of >1%. Miners 60–64 years of age have an incidence rate in excess of 2.5% annually. Lung cancer represents ~80% of all cancers seen annually among YTC employees, and mortality from this cancer is 10-fold higher in this area than the rest of China (14). For males >50 years of age, the lung cancer incidence rate is 3–7-fold higher than SEER rates for US males (15). This population has been exposed to a number of known carcinogens, including tobacco smoke, radon, and arsenic (16). The goal of the current study is to both explore the association between the *XRCC1* polymorphisms (individually and in combination) and the risk of lung cancer and to assess whether selected environmental exposures might serve to modify the risk of lung cancer associated with these polymorphisms.

## Materials and Methods

**Study Cohort.** A prospective cohort study of high-risk miners of the YTC was established in 1992 with annual follow-up through 1999. Eligible high-risk miners were ≥40 years of age with ≥10 years of underground mining and/or smelting experience and who were free of cancer (except for non-melanoma skin cancer) at baseline in 1992. The baseline and follow-up activities were added to an annual YTC screening of the miners ongoing since 1973. These activities included an interview about demographic, dietary, residential, occupational, and medical histories; a 24-h food recall; chest X-ray, physical exam; and sputum collection. The initial cohort established in 1992 had 6259 miners, and with each annual screen more miners entered the cohort as they reached the eligibility criteria, resulting in 9143 cohort members by 1997. During the annual screenings in 1993 and 1994, all miners were asked to provide

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[2] The abbreviations used are: XRCC1, X-ray repair cross-complementing group 1; YTC, Yunnan Tin Corporation: OR, odds ratio; CI, confidence interval.

a fasting blood specimen. Because of cultural taboos, only ~50% of 9143 participants provided blood. The sub-cohort that provided blood specimens was representative of the larger high-risk cohort. Lung cancer cases were ascertained by reports to the Cancer Registry of the Labor Protection Institute of the YTC or from the annual screens and were confirmed by the Joint National Cancer Institute/YTC Diagnosis Review Committee. Lung cancer cases were diagnosed by X-ray, sputum cytology, endoscopy, biopsy, and thoracotomy. Detailed descriptions of risk factors, criteria for lung cancer diagnoses, and histology of tumors have been published previously (14). More than 80% of the cases identified were classified as squamous cell carcinoma of the lung.

**Selection of Cases and Controls.** The cases consisted of 106 men and 2 women, 40–74 years of age, diagnosed with primary lung cancer during the years 1992–1997 among the sub-cohort of those who had given blood. Using incidence density sampling, we randomly selected controls from cohort participants who were alive and free of cancer at the time the matched cases were diagnosed. Controls were matched to cases on age (±2 years) and sex in a 2:1 ratio. Selection of cases and controls was independent of the assessment of XRCC1 genotype.

**Definition of Exposures.** All variables used in this study were derived from baseline evaluations. The cumulative radon exposure estimate for each subject was obtained by summing across the estimated working level months for each job held at the YTC prior to the date of entry at initial screening for the high-risk cohort. The cumulative individual arsenic exposure for each subject was estimated using an index for arsenic exposure (Index of Arsenic Exposure Months), which was calculated as a time weighted average of arsenic concentration ($mg/m^3$) times exposure months ($mg/m^3 \times$ months). Arsenic concentration ($mg/m^3$) was assessed in different work areas by measuring airborne arsenic dust levels. Individuals who had smoked cigarettes and/or pipes (water pipes or Chinese long-stem pipes) regularly for 6 months or longer at any time in their life were classified as ever smokers and were asked for information on a variety of smoking-related issues. Pack-year equivalents (g tobacco/day $\times$ years $\div$ 20) were used to measure cumulative tobacco consumption, which was calculated separately for cigarettes (1 cigarette = 1 g), water pipe, long-stem pipe, and total tobacco use (17). The tobacco exposure variables used in the current study were derived from the total tobacco (g/day) use variable and from years of smoking all tobacco products. Alcohol intake information, including alcohol from grain liquor, wine, and other spirits, was obtained by a single 24-h food and beverage recall questionnaire.

**Polymorphism Analyses.** All polymorphisms were analyzed using genomic DNA from lymphocytes using the ABI Prism 7700 sequence detector (TaqMan; PE Biosystems, Foster City, CA). PCR primers and dual-labeled allele discrimination probes were designed using PrimerExpress, version 1.0 (PE Biosystems). Probes were selected that had a predicted $T_m$ near 68°C, with the polymorphic base near the center. Flanking PCR primers were selected based on the calculated penalty score, $T_m$, length, and amplimer size. For the C-to-T polymorphism in exon 6, codon 194 "turbo" probes (with T = 5-propyne-2′-deoxyuridine) were used. Oligonucleotide sequences for the analyses were as follows:

Exon 6 codon 194:
Forward primer: GAGGATGAGAGCGCCAACTCT
Reverse primer: ACGTTGTCCGAGCTCACCTG
T allele probe: CTCTTCTTCAGCTGGATCAACAAGA
C allele probe: TCTTCTTCAGCCGGATCAACAAG

Exon 9, codon 280:
Forward primer: GACCCCCAGTGGTGCTAACC
Reverse primer: GCCTTCTCCTCGGGGTTTG
A allele probe: AGCTCCAACTCATACCCCAGCCACA
G allele probe: AGCTCCAACTCGTACCCCAGCCAC

Exon 10, codon 399:
Forward primer: GTAAGGAGTGGGTGCTGGACTGT
Reverse primer: GTCTGACTCCCCTCCAGATTCC
A allele probe: CTGCCCTCCCAGAGGTAAGGCCTC
G allele probe: CTGCCCTCCCGGAGGTAAGGCC

Genotyping reactions (10 μl) contained ~20 ng of genomic DNA, 1× TaqMan Master Mix, dual-labeled probes (100 nM each), and PCR primers (900 nM each). Reactions were performed in 96-well MicroAmp Optical reaction plates and caps (PE Biosystems). Plates were incubated at 50°C for 2 min and 95°C for 10 min, followed by 40 cycles of 95°C for 15 s and 62°C for 1 min. An annealing temperature of 64°C was used for the exon 6 assay. Reaction data were analyzed with Sequence Detection System, version 1.6.3. Amplified DNA from several individuals exhibiting each genotype was electrophoresed on an agarose gel to confirm amplimer size and sequenced to confirm each genotype. All lab personnel were blind to the case-control status of the samples. For quality control, genotype determinations were repeated for a random sample of 10% of study participants, and we observed a 100% concordance rate.

**Statistical Analyses.** The Wilcoxon rank-sum test was used to test the hypothesis that the distribution of baseline characteristics was the same for cases and controls. The $\chi^2$ test for heterogeneity was used for categorical variables to test the hypothesis that the distribution of allele prevalences was the same for cases and controls. Conditional logistic regression techniques were used to examine the association between genotype and lung cancer. Modification of the effect of genotype on lung cancer risk by age, radon exposure, arsenic exposure, and alcohol and tobacco consumption was examined by statistical tests of the first order interaction term in the logistic regression models. Statistical analyses stratified by environmental exposure were conducted by breaking the case-control

*Table 1* Risk factors for lung cancer comparing cases to controls[a]

| Risk factor | Cases ($n$ = 108) | Controls ($n$ = 216) | $P^b$ |
|---|---|---|---|
| Smoking status[c] | | | |
| Current | 87 (81%) | 152 (70%) | 0.12 |
| Former | 15 (14%) | 40 (19%) | |
| Never | 6 (5%) | 24 (11%) | |
| Cigarettes/day | 10 | 6 | <0.01 |
| Years of cigarette smoking | 42 | 40 | <0.08 |
| All tobacco smoked (g/day) | 17 | 13 | <0.01 |
| Years of water pipe smoking | 45 | 44 | <0.01 |
| Years of all tobacco smoking | 45 | 43 | <0.05 |
| Pack-year equivalents (all tobacco) | 34 | 25 | <0.01 |
| Alcohol (g/day) | | | |
| All men | 5 | 0 | 0.18 |
| Drinkers (48%) | 180 | 171 | 0.39 |
| Cumulative radon exposure (WLM)[d] | 570 | 408 | <0.05 |
| Cumulative arsenic exposure (IAEM) | 11,961 | 10,101 | 0.30 |
| Years mining/smelting jobs | 31 | 29 | <0.05 |

[a] Based on unmatched data with continuous variables expressed as the median.
[b] $P$ as determined by Wilcoxon rank-sum tests and $\chi^2$ for smoking status.
[c] Smoking status shown as number of individuals in each category.
[d] WLM, working level months; IAEM, Index of Arsenic Exposure months.

*Table 2* Association between the XRCC1 polymorphisms and lung cancer risk[a]

| XRCC1 genotype | Cases, *n* (%) | Controls, *n* (%) | $\chi^2$ *P* | OR | |
|---|---|---|---|---|---|
| | | | | Unadjusted | Adjusted |
| Exon 6, codon 194 | | | | | |
| Arg/Arg | 52 (48%) | 85 (40%) | | 1.0 (Ref)[b] | 1.0 (Ref) |
| Arg/Trp | 47 (44%) | 104 (50%) | 0.42 | 0.7 (0.4–1.2) | 0.7 (0.4–1.2) |
| Trp/Trp | 9 (8%) | 21 (10%) | | 0.7 (0.3–1.6) | 0.7 (0.3–1.8) |
| Arg/Trp + Trp/Trp | 56 (52%) | 125 (60%) | 0.19 | 0.7 (0.5–1.2) | 0.7 (0.4–1.2) |
| Exon 9, codon 280 | | | | | |
| Arg/Arg | 83 (78%) | 177 (85%) | | 1.0 (Ref) | 1.0 (Ref) |
| Arg/His | 20 (19%) | 32 (15%) | 0.03 | 1.4 (0.7–2.6) | 1.6 (0.8–3.1) |
| His/His | 3 (3%) | 0 (0%) | | NC[c] | NC |
| Arg/His + His/His | 23 (22%) | 32 (15%) | 0.16 | 1.6 (0.9–2.9) | 1.8 (1.0–3.4) |
| Exon 10, codon 399 | | | | | |
| Arg/Arg | 59 (55%) | 117 (54%) | | 1.0 (Ref) | 1.0 (Ref) |
| Arg/Gln | 40 (37%) | 80 (37%) | 0.74 | 1.0 (0.6–1.6) | 1.0 (0.6–1.6) |
| Gln/Gln | 8 (7%) | 11 (5%) | | 1.4 (0.5–3.7) | 1.3 (0.5–3.5) |
| Arg/Gln + Gln/Gln | 48 (44%) | 91 (42%) | 0.85 | 1.0 (0.6–1.6) | 1.0 (0.6–1.6) |

[a] All conditional logistic regression models adjusted for radon and tobacco exposure (pack-year equivalents) modeled as a continuous term.
[b] Ref, used as reference group.
[c] NC, OR not calculable with conditional logistic regression (all 3 homozygous variant individuals developed lung cancer).

*Table 3* Association between XRCC1 genotype profile and lung cancer risk

| Exon 6 | Exon 9 | Exon 10 | Cases | Controls | OR (95% CI; *P*) | |
|---|---|---|---|---|---|---|
| | | | | | Unadjusted | Adjusted[a] |
| All wild-type genotypes | | | | | | |
| WT[b] | WT | WT | 13 | 30 | 1.0 (Reference)[c] | 1.0 (Reference)[c] |
| One variant polymorphism | | | | | | |
| VT | WT | WT | 28 | 63 | 1.1 (0.5–2.4; 0.76) | 1.2 (0.6–2.5; 0.67) |
| WT | VT | WT | 9 | 8 | 2.9 (0.9–8.8; 0.06) | 2.9 (0.9–9.2; 0.07) |
| WT | WT | VT | 23 | 38 | 1.5 (0.7–3.4; 0.29) | 1.6 (0.7–3.5; 0.28) |
| Two variant polymorphisms | | | | | | |
| VT | VT | WT | 8 | 16 | 1.2 (0.5–3.6; 0.66) | 1.3 (0.5–3.9; 0.59) |
| WT | VT | VT | 6 | 8 | 1.9 (0.6–6.4; 0.30) | 2.0 (0.6–7.1; 0.32) |
| VT | WT | VT | 19 | 45 | 1.1 (0.5–2.4; 0.87) | 1.1 (0.5–2.4; 0.87) |
| Three variant polymorphisms | | | | | | |
| VT | VT | VT | 0 | 0 | — | — |

[a] All unconditional logistic regression models adjusted for age, sex, radon and tobacco exposure (pack-year equivalents) modeled as a continuous term.
[b] WT, homozygous wild type; VT, heterozygous and homozygous variant.
[c] Used as reference group.

match to avoid the loss of subjects due to splitting of matched sets that fell into different strata and using unconditional logistic regression adjusted for age and sex (the original matching criteria) and other potential confounders.

Potential confounding of the association between genotype and cancer risk by other related risk factors was explored using Spearman rank correlation analysis and multivariate logistic regression models, including stepwise regression models both before and after stratification. If the potential confounder caused a significant change in the log likelihood estimate ($P < 0.05$) and a >20% change in the $\beta$ coefficient, it was kept in the model for further multivariate analysis.

Among cases and controls in our study, 48% were alcohol drinkers (50% cases and 48% controls), and almost all alcohol consumed was in the form of grain liquor. To avoid potential misclassification of the amount of alcohol consumed, we restricted our analysis to alcohol drinker status. Our alcohol data is based on 24-h recall questionnaire, which gives a better estimate of drinker status than actual consumption. Exclusion of early cases (diagnosed within 1 year of blood draw) did not materially alter any of the risk estimates. All analyses were performed using the statistical software package STATA (STATA Corporation, College Station, TX).

## Results

The median age of cases and controls was 63 years, and most were retired (99%). Comparison of lifestyle and occupational variables that could be related to cancer risk yielded some differences between cases and controls (Table 1). As expected, tobacco use and radon exposure were significantly higher in the cases than in the controls. The cases had also performed mining and smelting work longer than the controls. Detailed analyses of these risk factors and lung cancer risk in the YTC cohort have been published previously (14).

The distribution of XRCC1 variant alleles and their association with the risk of lung cancer are shown in Table 2. There was a suggestion of a protective effect for the *XRCC1* Arg194Trp variant allele, but no association for the Arg399Gln variant allele and lung cancer risk. The Arg280His variant allele was associated with increased lung cancer risk (OR, 1.8; 95% CI, 1.0–3.4) after adjusting for radon and tobacco expo-

*Table 4* Stratified analyses of the association between XRCC1 variants and lung cancer risk[a]

| | Arg194Trp[b] | | Arg280His[b] | | Arg399Gln[b] | |
|---|---|---|---|---|---|---|
| | WT[c]-Arg OR [Cases/Controls] | VT-Trp OR (95% CI) [Cases/Controls] | WT-Arg OR [Cases/Controls] | VT-His OR (95% CI) [Cases/Controls] | WT-Arg OR [Cases/Controls] | VT-Gln OR (95% CI) [Cases/Controls] |
| Alcohol (g/day) | | | | | | |
| Nondrinkers (0) | 1 [21/48] | 1.1 (0.5–2.1) [33/63] | 1 [44/87] | 0.8 (0.3–1.9) [9/23] | 1 [32/58] | 0.8 (0.4–1.5) [22/52] |
| Drinkers (>10) | 1 [31/37] | 0.4 (0.2–0.9) [23/62] | 1 [39/90] | 3.7 (1.5–9.5) [14/9] | 1 [27/59] | 1.2 (0.5–2.6) [26/39] |

[a] All unmatched logistic regression models adjusted for age at baseline, sex, radon exposure, and tobacco exposure (pack-year equivalents).
[b] *P* for interaction for alcohol: Arg194Trp, 0.04; Arg280His, 0.02; Arg399Gln, 0.18.
[c] WT, homozygous wild-type; VT, heterozygous and homozygous variant.

sure. All three individuals that were homozygous variants for the Arg280His polymorphism developed cancer in our study. There were no homozygous variants among the controls; consequently, an OR could not be computed for the association between the homozygous Arg280His variant and risk of lung cancer. Adjustment for baseline covariates, such as arsenic exposure, that could be associated with lung cancer risk did not materially alter the risk estimates (data not shown). The risk estimates shown in Table 2 were adjusted for tobacco use (pack-year equivalents) and radon exposure because they were significantly associated with lung cancer risk.

Haplotype analyses of the three *XRCC1* polymorphisms are shown in Table 3. Assessment of intra-gene interactions in the logistic regression models of the three *XRCC1* polymorphisms revealed no statistically significant interactions. The only association observed was that of the Arg280His variant alone compared with wild-type for all three genotypes and lung cancer risk at the margin of statistical significance with an OR of 2.9 ($P = 0.07$).

The association between the three *XRCC1* polymorphisms and lung cancer risk stratified by alcohol drinker status (Table 4) was used to explore the modification of the effect of genotype by alcohol consumption. We also examined effect modification by other important exposure variables such as tobacco smoking, radon, and arsenic, and with the exception of tobacco smoking observed no statistically significant interactions. Further examination of the putative interaction between the Arg194Trp and smoking ($P = 0.05$) indicated that it was spurious [failed to meet the independence test of genotype and exposure among the controls ($P = 0.015$)]. Alcohol drinkers with the Arg194Trp variant allele seemed to be at lower risk for lung cancer than those with the wild-type allele (*P* for interaction = 0.04). Conversely, alcohol drinkers with the Arg280His allele were at 3.7-fold greater risk of lung cancer than those with the homozygous wild-type genotype (*P* for interaction = 0.02).

## Discussion

DNA repair systems act to maintain genomic integrity in the face of environmental insults, cumulative effects of age, and general DNA replication errors. XRCC1 is thought to play a role in the multistep base excision repair pathway where "nonbulky" base adducts produced by methylation, oxidation, reduction, or fragmentation of bases by ionizing radiation or oxidative damage are removed (18). Although the specific function of XRCC1 has not been identified, it is believed that XRCC1 complexes with DNA ligase III via a BRCT domain in its COOH terminus and with DNA polymerase $\beta$ in its $NH_2$ terminus to repair gaps left during base excision repair (13).

Lack of XRCC1 activity in mice is an embryo-lethal condition. Thus, it can be assumed that the three human *XRCC1* polymorphisms do not cause complete loss of protein function. There currently are no reports on the association between *XRCC1* polymorphisms and lung cancer risk. The Arg194Trp and Arg280His amino acid substitutions reside in the linker region separating the DNA polymerase $\beta$ domain from the poly(ADP-ribose) polymerase-interacting domain. The Arg399Gln change occurs in the COOH-terminal side of the poly(ADP-ribose) polymerase-interacting domain and within an identified BRCT domain (9). Amino acid substitutions in the BRCT domain and in the DNA polymerase $\beta$-interacting domain in the hamster have been reported to disrupt the functionality of XRCC1 (19).

Our findings suggest that the *XRCC1* Arg280His polymorphism is associated with the risk of lung cancer. Individuals with the variant allele were at 80% greater risk compared with those with the homozygous wild-type genotype after adjustment for radon and tobacco exposure. In addition, although the numbers were small in our population, all three individuals with the homozygous variant genotype developed lung cancer. Haplotype analyses also confirmed this finding, where individuals with the Arg280His variant alone were at almost 3-fold ($P = 0.07$) greater risk of lung cancer compared with individuals who were wild-type for all three *XRCC1* polymorphisms. The polymorphisms at codons 194 and 399 were not associated with lung cancer risk in our study. In fact, individuals with the Arg194Trp substitution allele seemed to be at reduced risk of lung cancer, although the risk estimates were not statistically significant (OR, 0.7; 95% CI, 0.43–1.16). This finding is consistent with that reported by Sturgis *et al.* (20), where the Arg194Trp polymorphism was associated with a reduction in risk of squamous cell carcinoma of the pharynx and oral cavity, another cancer related to tobacco and alcohol consumption.

XRCC1 may be involved in base excision repair of genomic damage attributable to environmental exposure to carcinogens such as tobacco or alcohol. We observed a statistically significant interaction between cumulative tobacco exposure and the Arg194Trp polymorphism ($P = 0.05$). However, this interaction was apparently driven by an association between the Arg194Trp polymorphism and smoking ($P = 0.015$) among the controls and failed to meet the test of independence of genotype and environmental exposure among the controls.

Alcohol drinking apparently modified the effect of the Arg194Trp and the Arg280His polymorphisms on lung cancer risk. Among alcohol drinkers, the Arg194Trp variant allele reduced the risk of lung cancer compared with individuals with the homozygous wild-type genotype. The Arg194Trp variant may be able to enhance DNA repair activity, leading to reduced risk of lung cancer compared with those with the homozygous

wild-type genotype. Conversely, among alcohol drinkers the Arg280His polymorphism increased the risk of lung cancer compared with those with the homozygous wild-type genotype. Apparently, unlike the Arg194Trp polymorphism, the Arg280His polymorphism may result in lower DNA repair ability compared with homozygous wild type. However, because of the small sample size of our study group, these observation need to be interpreted with caution. A plausible explanation for our observations of "alcohol interactions" with *XRCC1* Arg194Trp and Arg280His polymorphisms may be just chance.

One of the strengths of this study is its prospective design. The collection of covariate data (*e.g.*, smoking and alcohol) before case diagnosis minimized the potential for recall bias for measures of environmental exposures, and the availability of these data also allowed us to explore gene-environment interactions. One of the limitations of our study, as mentioned earlier, was its rather small sample size. The generalizability of these results may also be somewhat restricted because the study was conducted among a rather unique group of tin miners. Other studies examining the effects of *XRCC1* and other DNA repair polymorphisms and lung cancer risk are clearly needed.

In summary, this is the first observational study to examine the association between the three polymorphisms of *XRCC1* and risk of lung cancer. Our data suggest a modest elevated risk for lung cancer in individuals with the Arg280His *XRCC1* polymorphism.

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